US005538975A

United States Patent [19]

Dionne

[11] Patent Number: 5,538,975

[45] Date of Patent: Jul. 23, 1996

[54] 1,3-OXATHIOLANE NUCLEOSIDE COMPOUNDS AND COMPOSITIONS

[75] Inventor: Gervais Dionne, Laval, Canada

[73] Assignee: BioChem Pharma, Inc., Laval, Canada

[21] Appl. No.: 190,203

[22] PCT Filed: Jul. 24, 1992

[86] PCT No.: PCT/CA92/00321

§ 371 Date: Feb. 1, 1994

§ 102(e) Date: Feb. 1, 1994

[87] PCT Pub. No.: WO93/03027

PCT Pub. Date: Feb. 18, 1993

[30] Foreign Application Priority Data

Aug. 1, 1991 [GB] United Kingdom 9116601

[51] Int. Cl.[6] C07D 411/04, A61K 31/505

[52] U.S. Cl. 514/256; 514/49; 514/50; 514/269; 514/274; 536/4.1; 544/242

[58] Field of Search 536/4.1; 514/23, 514/24, 49, 274, 85, 256, 269; 544/242

[56] References Cited

U.S. PATENT DOCUMENTS

4,366,381	6/1982	Nagata et al.	544/313
5,047,407	9/1991	Belleau et al.	514/274
5,204,466	4/1993	Liotta et al.	544/317
5,210,085	5/1993	Liotta et al.	514/274
5,248,776	9/1993	Chu et al.	544/310
5,270,315	12/1993	Belleau et al.	514/262
5,276,151	1/1994	Liotta	544/317
5,444,063	8/1995	Schinazi	514/262
5,466,806	11/1995	Belleau et al.	544/310

FOREIGN PATENT DOCUMENTS

0382526	8/1990	European Pat. Off. .	
WO91/11186	8/1991	WIPO	514/274
WO91/17159	11/1991	WIPO	514/274
WO92/10496	6/1992	WIPO	514/274
WO92/14743	9/1992	WIPO	514/274
WO92/15308	9/1992	WIPO	514/274
WO92/15309	9/1992	WIPO	514/274
WO92/18517	10/1992	WIPO	514/274
9221676	12/1992	WIPO .	
WO93/03027	2/1993	WIPO	514/274
9414802	7/1994	WIPO .	

OTHER PUBLICATIONS

Doong, et al. "Inhibition of the Replication of Hepatitis B Virus In Vitro by 2',3'-Dixeoxy-3'-Thiacytidine and Related Analogues", *Proc. Natl. Acad. Sci U.S.A.*, vol. 88(19), pp. 8495–8499 (1991).

Jeong, et al. "Structure-Activity Relationships of β-D-(2S, 5R)-and α-D-(2S,5R)-1,3-Oxathiolanyl Nucleosides as Potential Anti-HIV Agents", *J. Med. Chem.*, vol. 36, pp. 2627–2638 (1993).

Jeong et al., "Asymmetric Synthesis and Biological Evaluation of β-L-(2R,5S)-and α-L-(2R,5R)-1,3-Oxathiolane-Pyrimidine and -Purine Nucleosides as Potential Anti-HIV Agents", *J. Med. Chem.*, vol. 36(2) pp. 181–195 (1993).

Frick, et al., "Pharmakokinetics, Oral Bioavailability, and Metabolic Disposition in Rats of (−)-*cis*-5-Fluoro-1-[2-(Hydroxymethyl)-1,3-Oxathiolan-5-yl]Cytosine, a Nucleoside Analog Active Against Human Immunodeficiency Virus and Hepatitis B Virus", *Antimicrob. Agents & Chemother.*, vol. 37(11), pp. 2285–2292 (1993).

Furman, et al., "The Anti-Hepatitis B Virus Activities, Cytotoxicities, and Anabolic Profiles of the (−) and (+) Enantiomers of cis-5-Fluoro-1-[2-(Hydroxymethyl)-1, 3-Oxathiolan-5-yl]Cytosine", *Antimicrob. Agents & Chemother.*, vol. 36(12), pp. 2686–2692 (1992).

Chang et al., J. of Biol. Chemistry, vol. 267, No. 31, pp. 22414–22420, Nov. 5, 1992.

Primary Examiner—James O. Wilson

Attorney, Agent, or Firm—Fish & Neave; James F. Haley, Jr.; Leslie A. McDonell

[57] ABSTRACT

The invention relates to 1,3-oxathiolane nucleoside analogues and their use in the treatment of viral infections. More specifically, this invention relates to (−)-4-amino-5-fluoro-1-(2-hydroxymethyl-1,3-oxathiolan-5-yl)-(1H)-pyrimidin-2-one and pharmaceutically acceptable derivatives and pharmaceutical formulations thereof.

5 Claims, No Drawings